FIG. 1

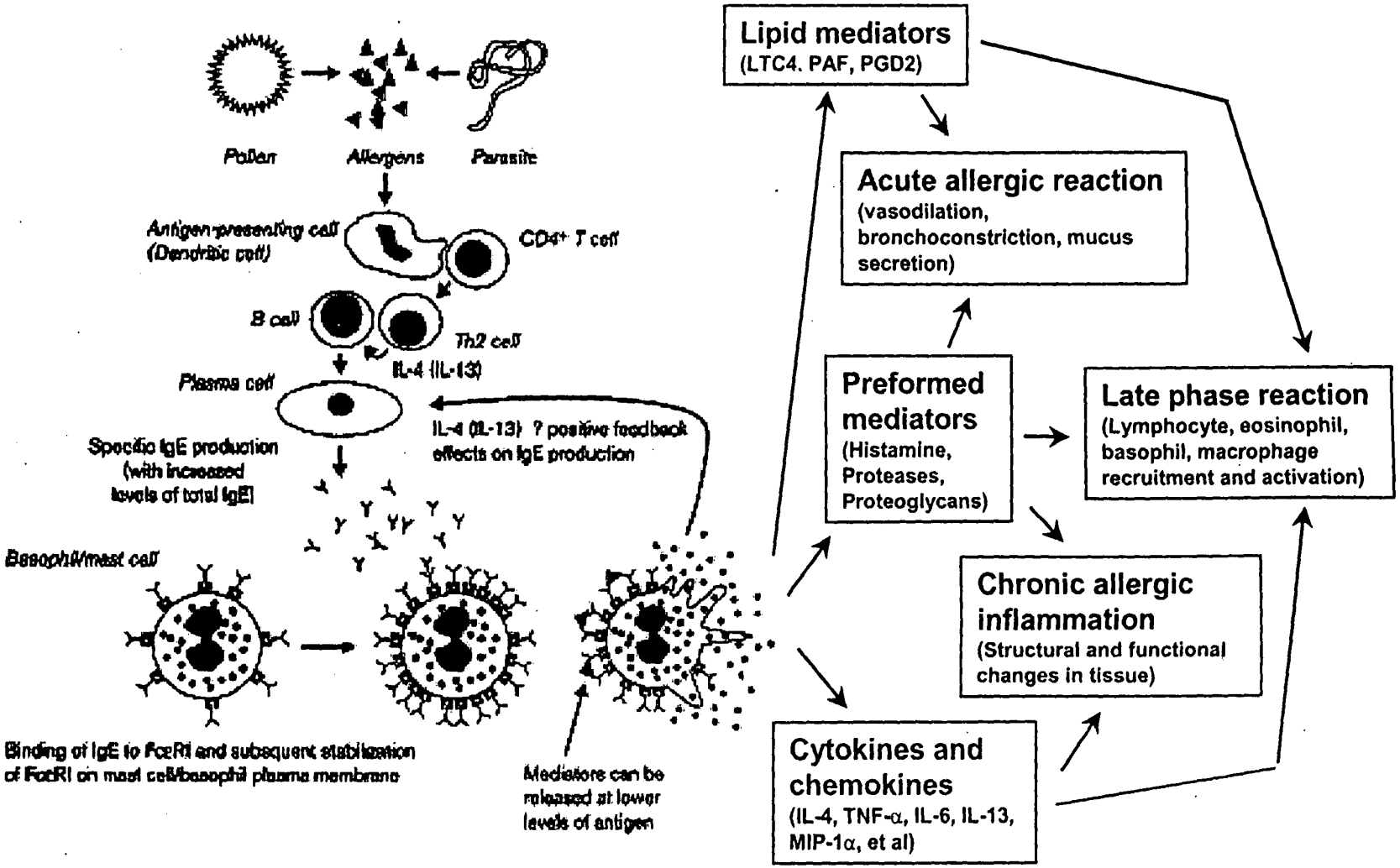

Pollen
Allergens
Parasite
Antigen-presenting cell (Dendritic cell)
CD4+ T cell
B cell
Th2 cell
IL-4 (IL-13)
Plasma cell
Specific IgE production (with increased levels of total IgE)
IL-4 (IL-13) ? positive feedback effects on IgE production
Basophil/mast cell
Binding of IgE to FcεRI and subsequent stabilization of FcεRI on mast cell/basophil plasma membrane
Mediators can be released at lower levels of antigen
Lipid mediators
(LTC4. PAF, PGD2)
Acute allergic reaction
(vasodilation, bronchoconstriction, mucus secretion)
Preformed mediators
(Histamine, Proteases, Proteoglycans)
Late phase reaction
(Lymphocyte, eosinophil, basophil, macrophage recruitment and activation)
Chronic allergic inflammation
(Structural and functional changes in tissue)
Cytokines and chemokines
(IL-4, TNF-α, IL-6, IL-13, MIP-1α, et al)

FIG. 2

Mast Cell FceR1 Signaling Pathway

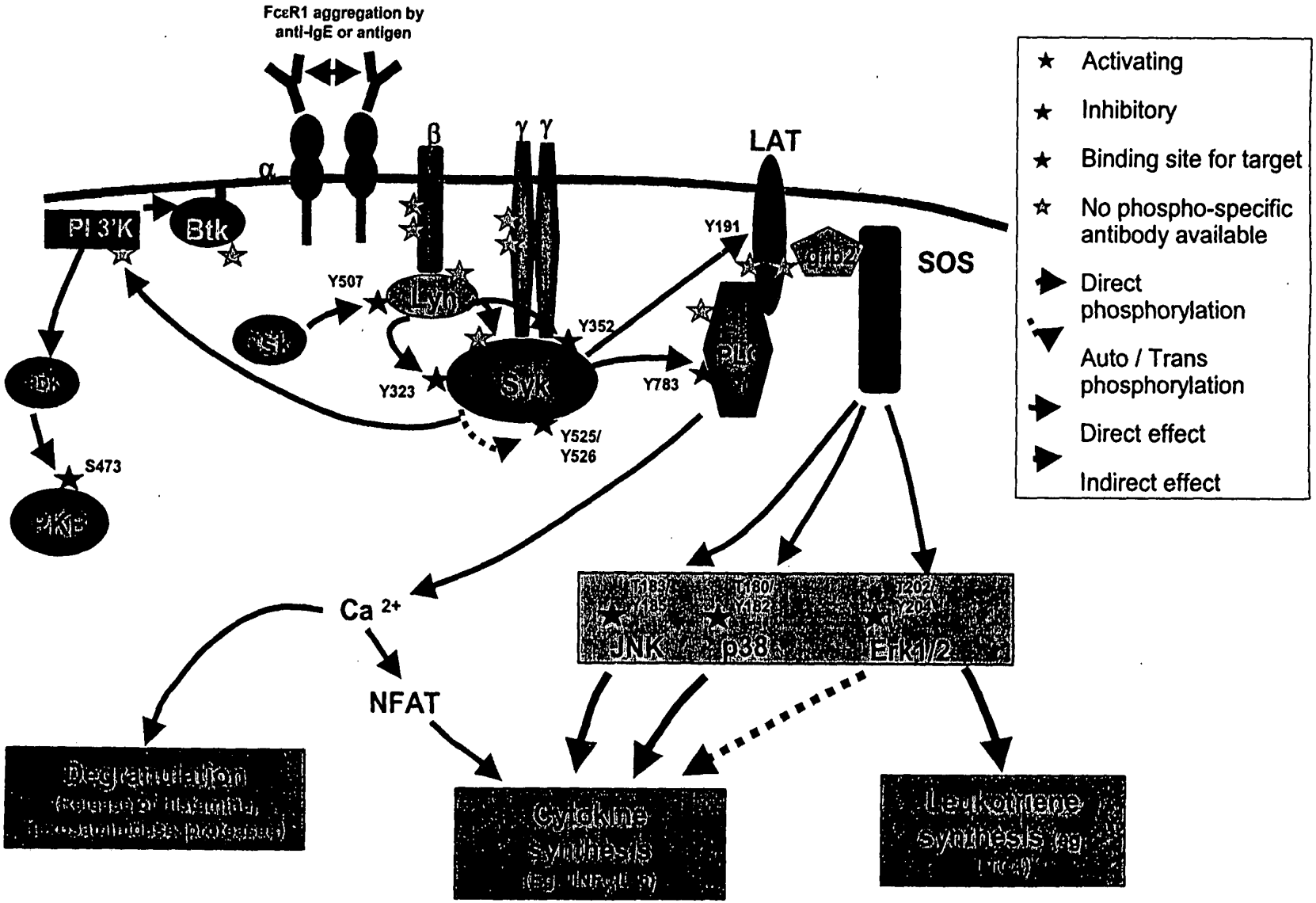


FIG. 3

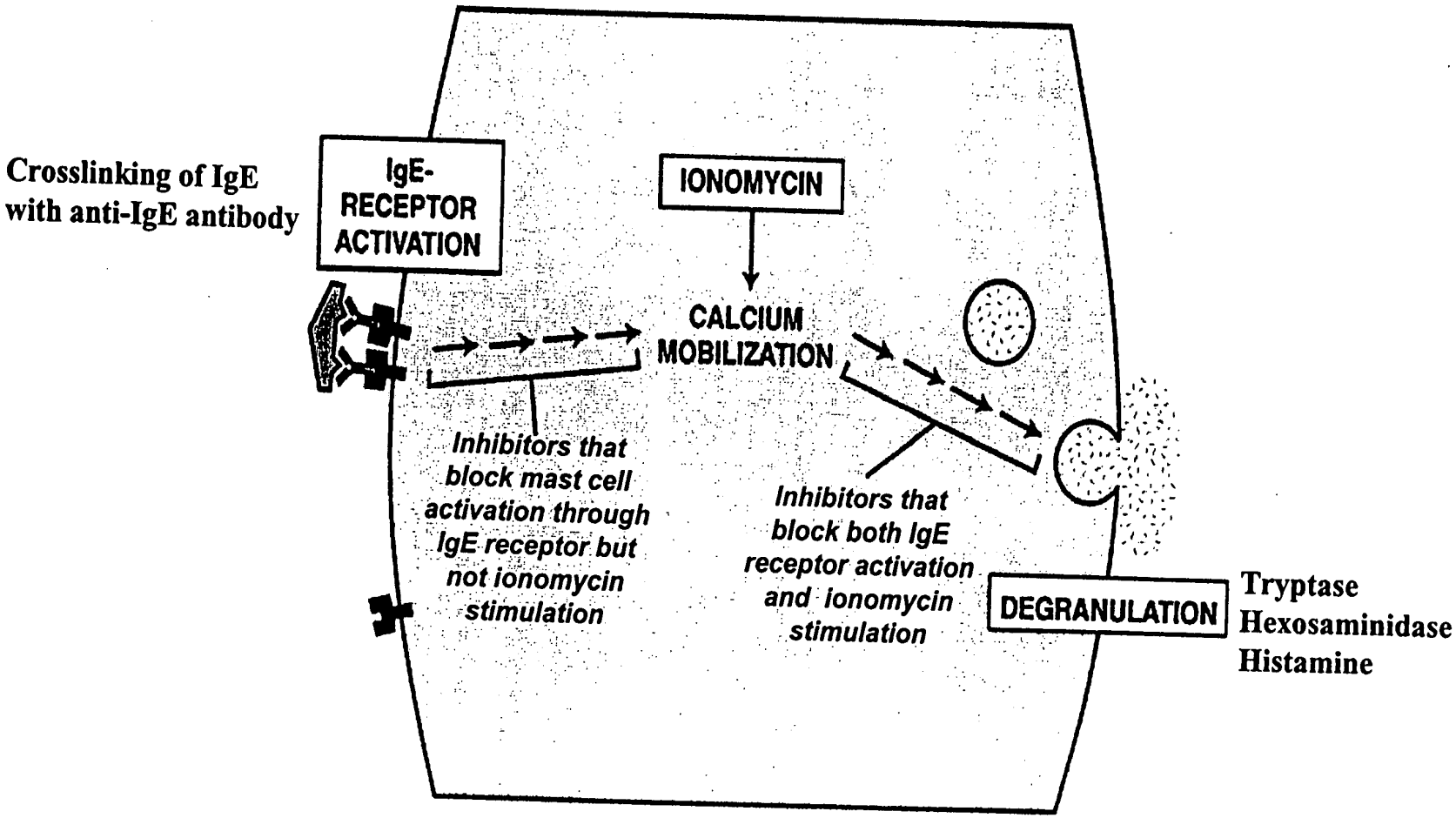

Crosslinking of IgE with anti-IgE antibody
IgE-RECEPTOR ACTIVATION
IONOMYCIN
CALCIUM MOBILIZATION
Inhibitors that block mast cell activation through IgE receptor but not ionomycin stimulation
Inhibitors that block both IgE receptor activation and ionomycin stimulation
DEGRANULATION
Tryptase
Hexosaminidase
Histamine

FIG. 4

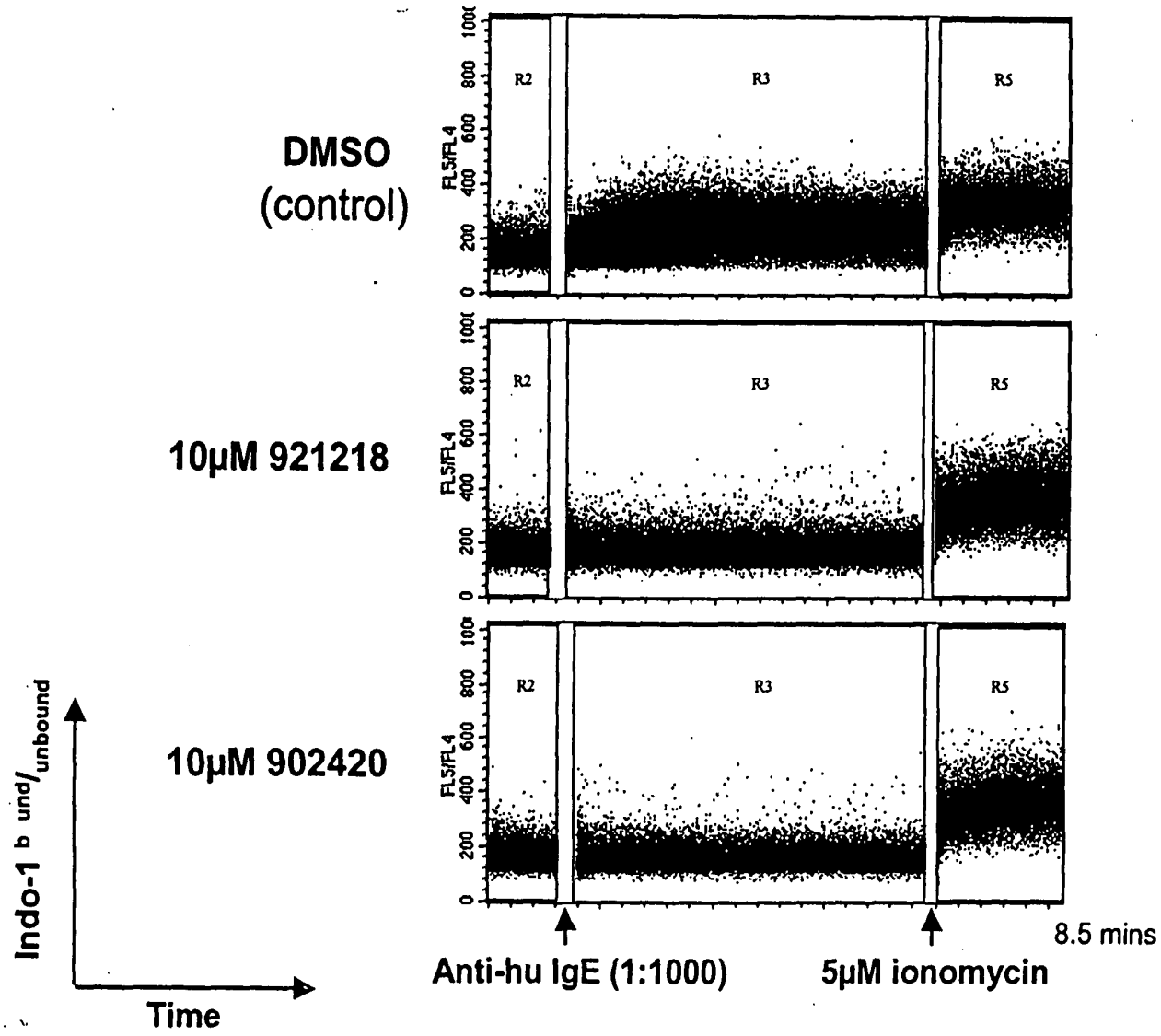

DMSO
(control)
10μM 921218
10μM 902420
R2
R3
R5
FL5/FL4
0
200
400
600
800
1000
Indo-1 b und/unbound
Time
Anti-hu IgE (1:1000)
5μM ionomycin
8.5 mins

FIG. 5

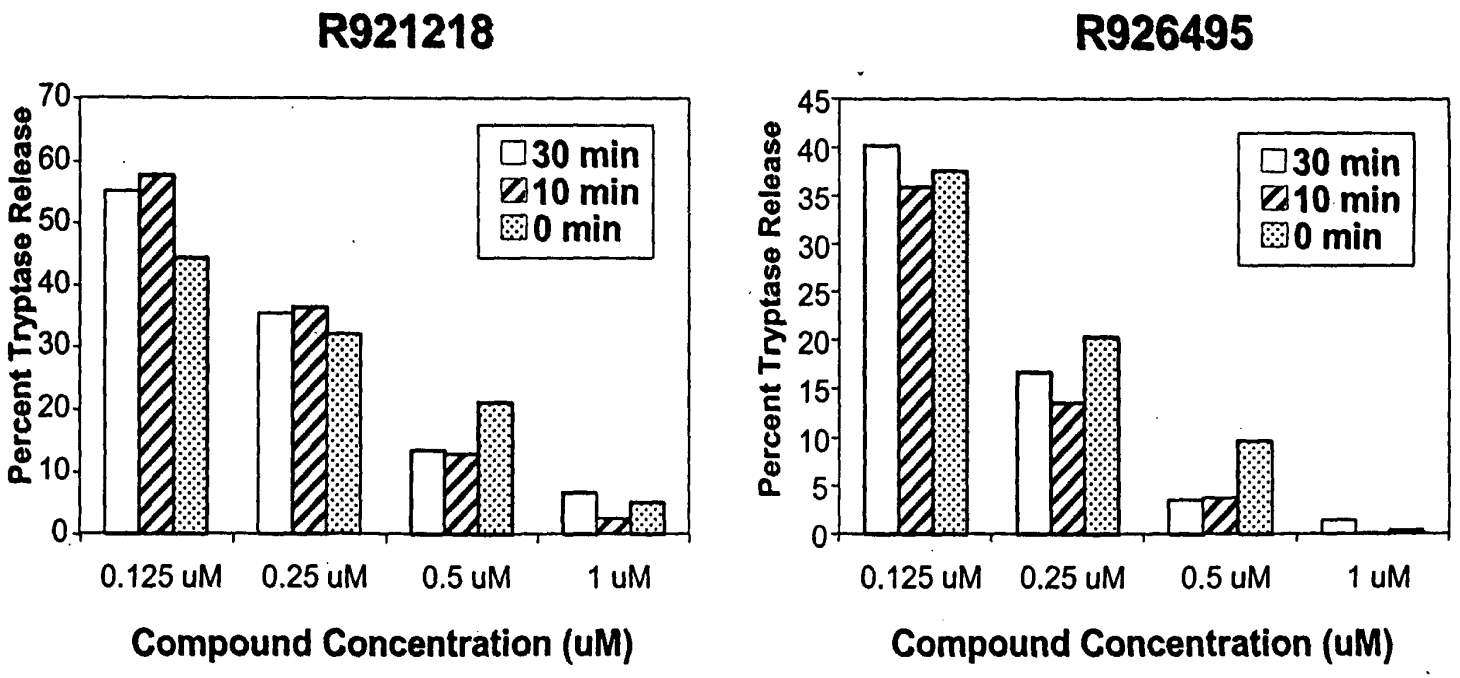

R921218
Percent Tryptase Release
70
60
50
40
30
20
10
0
30 min
10 min
0 min
0.125 uM
0.25 uM
0.5 uM
1 uM
Compound Concentration (uM)
R926495
Percent Tryptase Release
45
40
35
30
25
20
15
10
5
0
30 min
10 min
0 min
0.125 uM
0.25 uM
0.5 uM
1 uM
Compound Concentration (uM)

FIG. 6

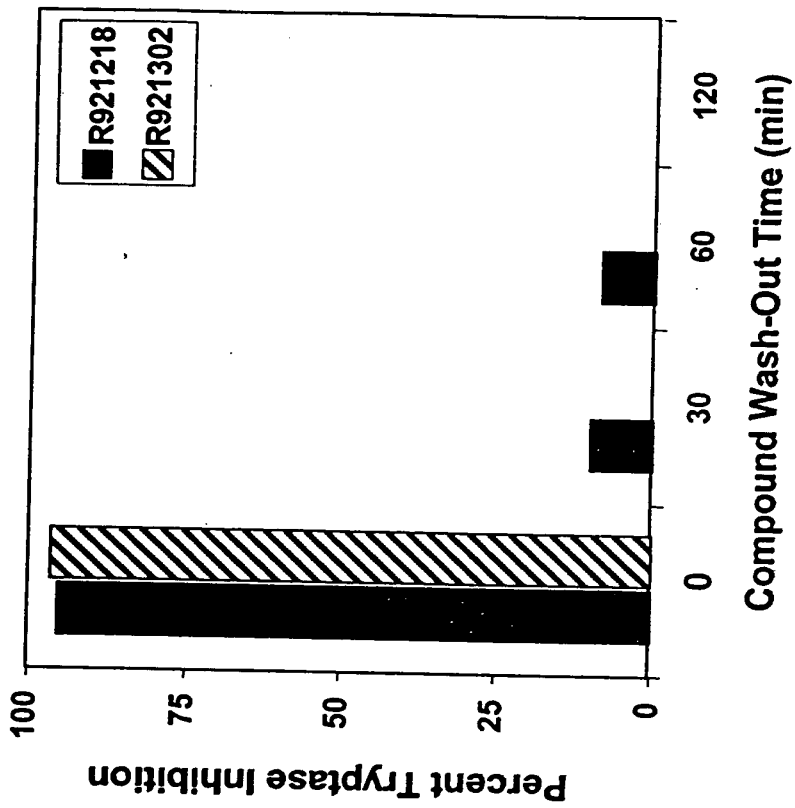

R921218
R921302
Percent Tryptase Inhibition
100
75
50
25
0
0
30
60
120
Compound Wash-Out Time (min)

FIG. 7

Inhibition of Phosphorylation of Proteins Downstream of Syk Kinase in Fce Receptor Activated BMMC Cells

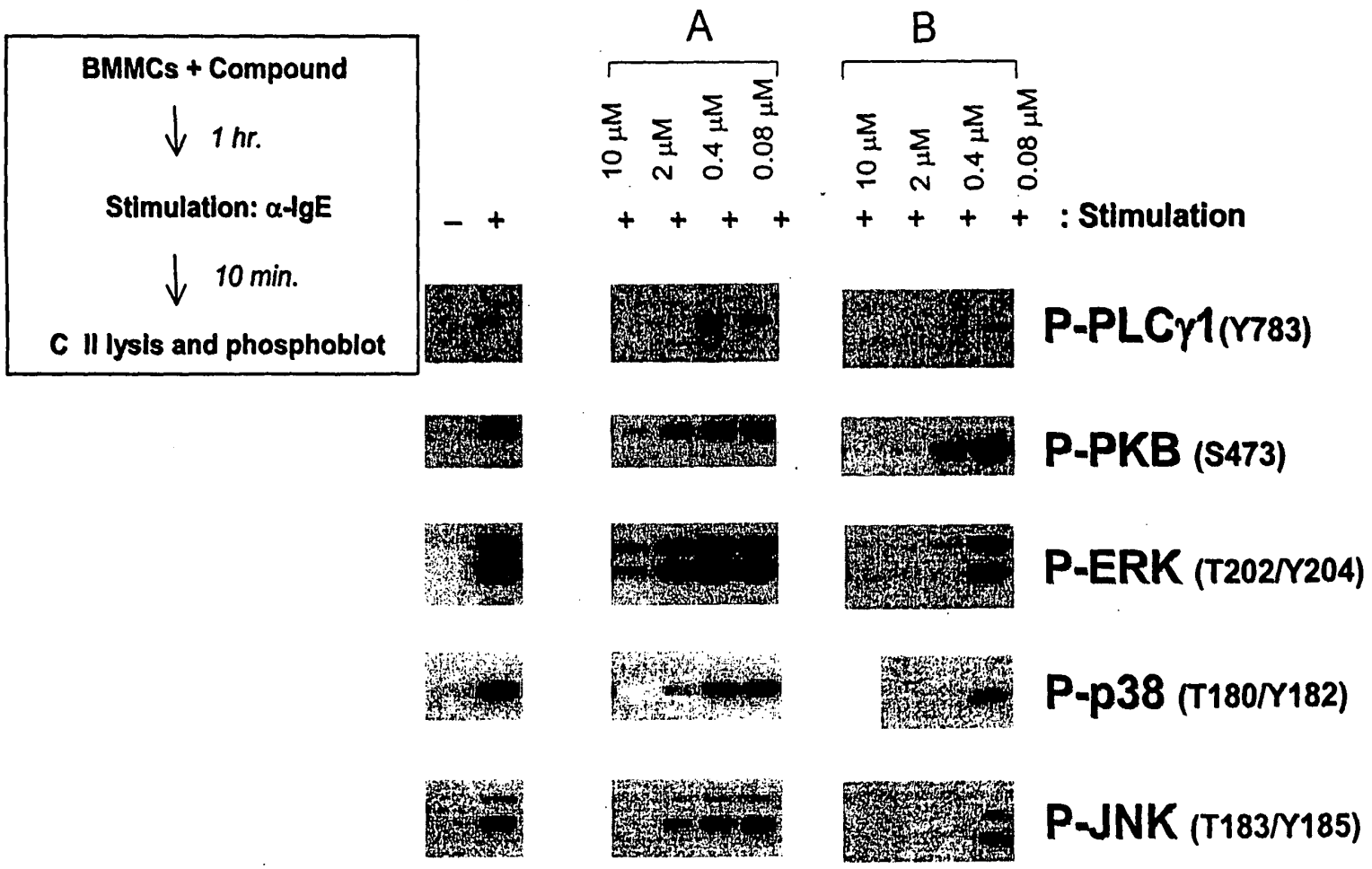
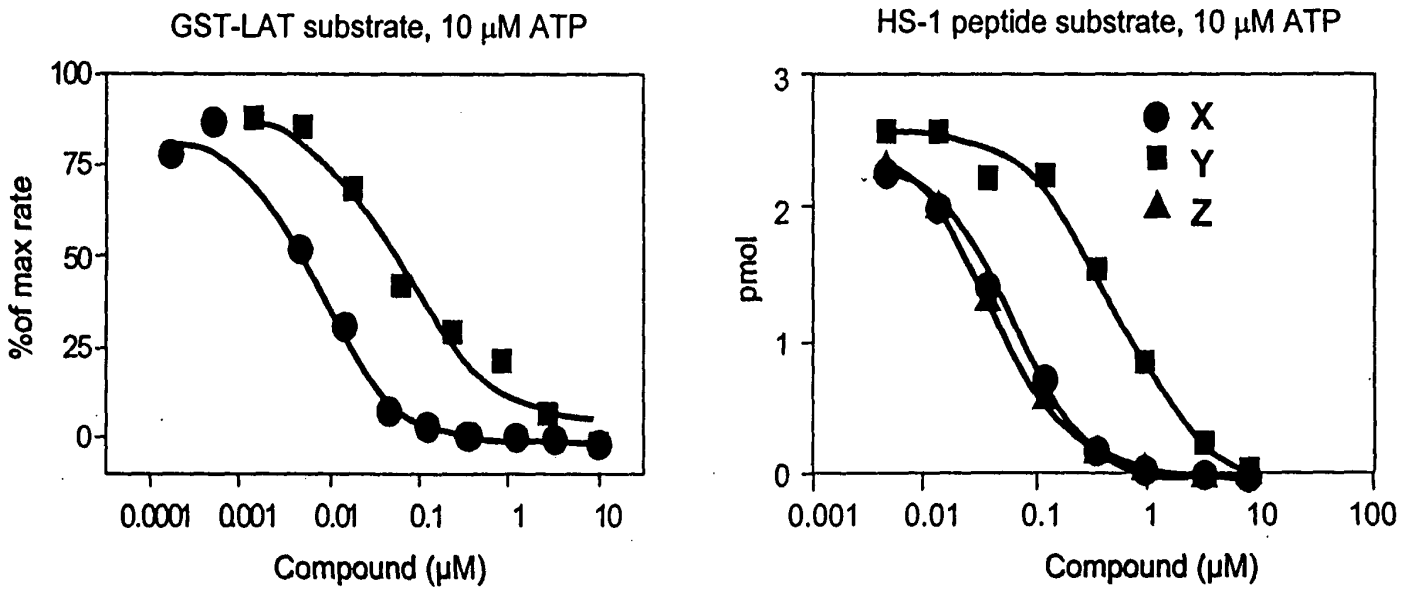


FIG. 8

The Disclosed Compounds Potently Inhibit the Activity of Syk Kinase

Human Syk kinase
***In vitro* Fluorescence Polarization Kinase Assay**

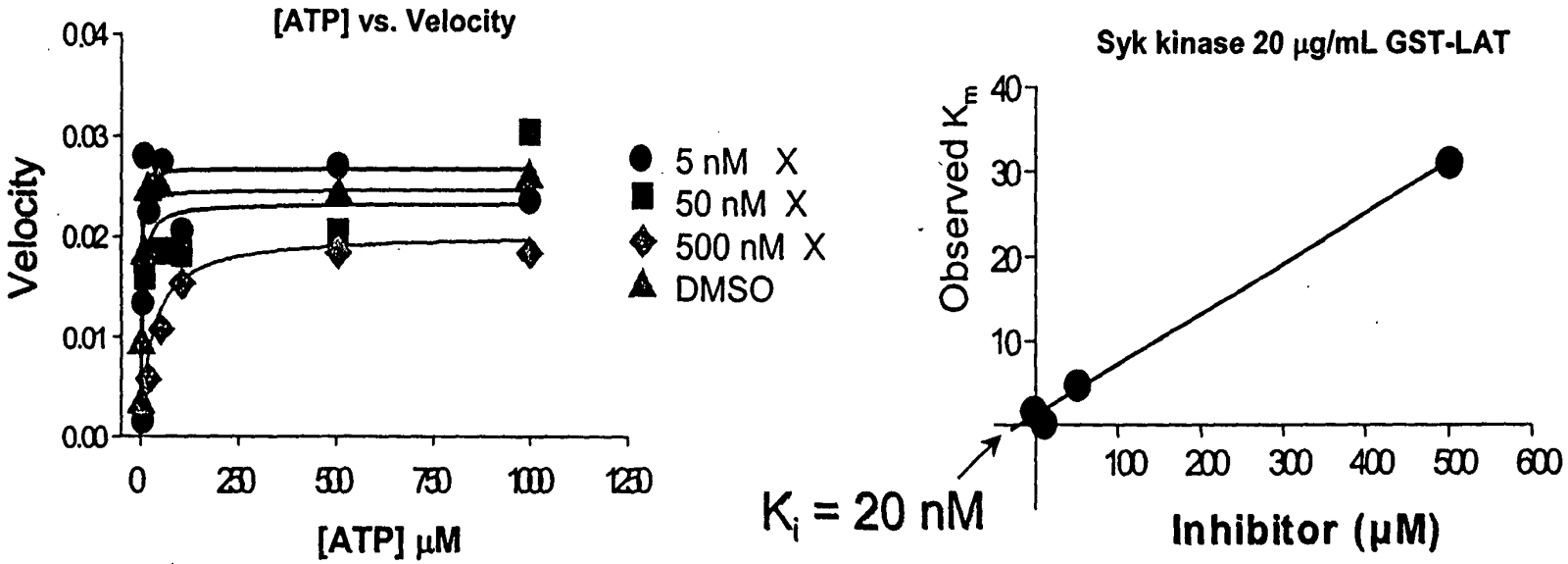


IC_{50} (nM)

	GST-LAT	HS-1
Y	200	570
X	10	62
Z	ND	43

FIG. 9

Compound Inhibition of Syk is ATP Competitive



	DMSO	5 nM X	50 nM X	500 nM X
V_{max}	.025	0.027	.023	0.020
K_m	1.54	0.79	4.5	31

CHMC: Cultured human mast cells

FIG. 10

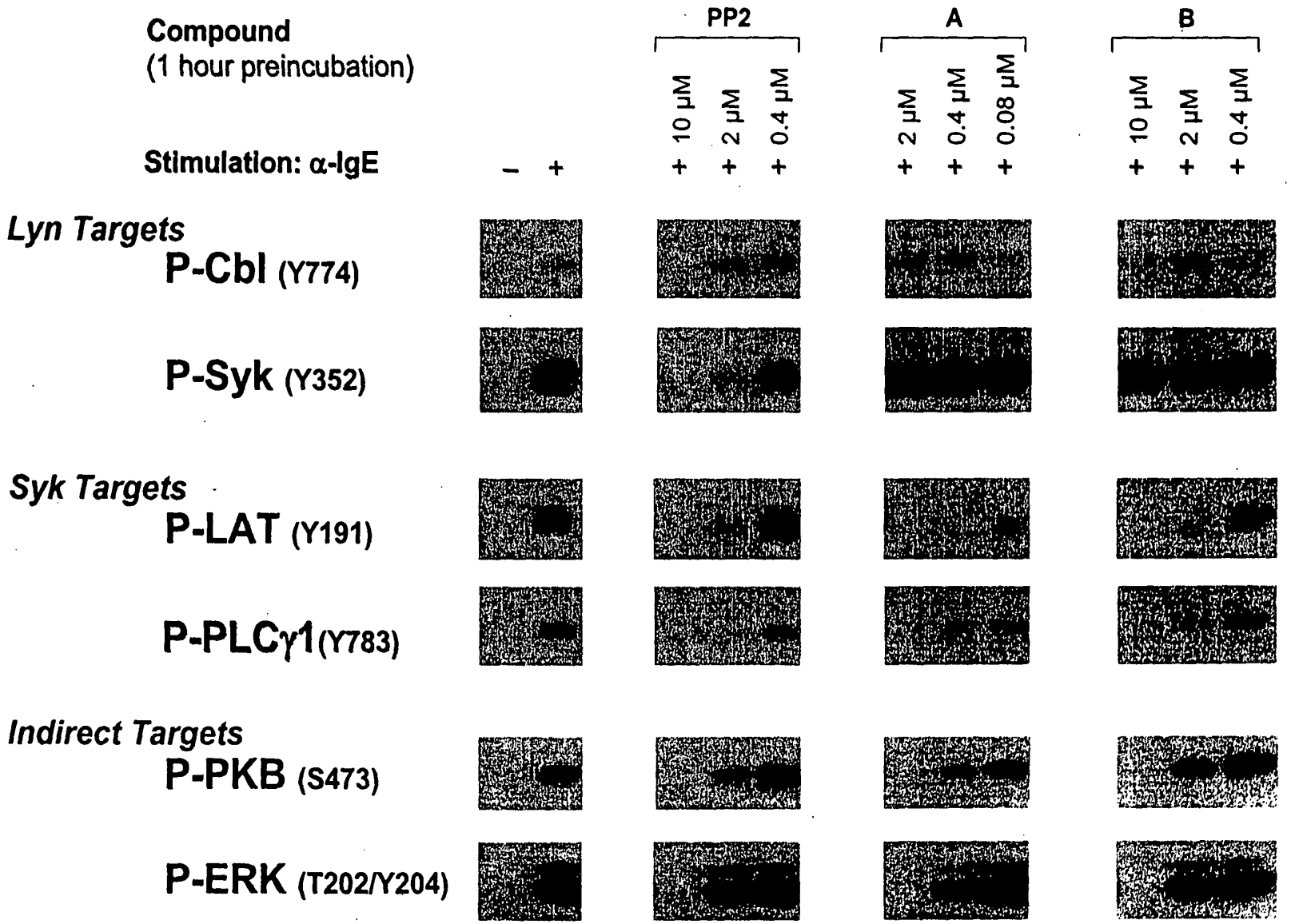


FIG. 11A

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

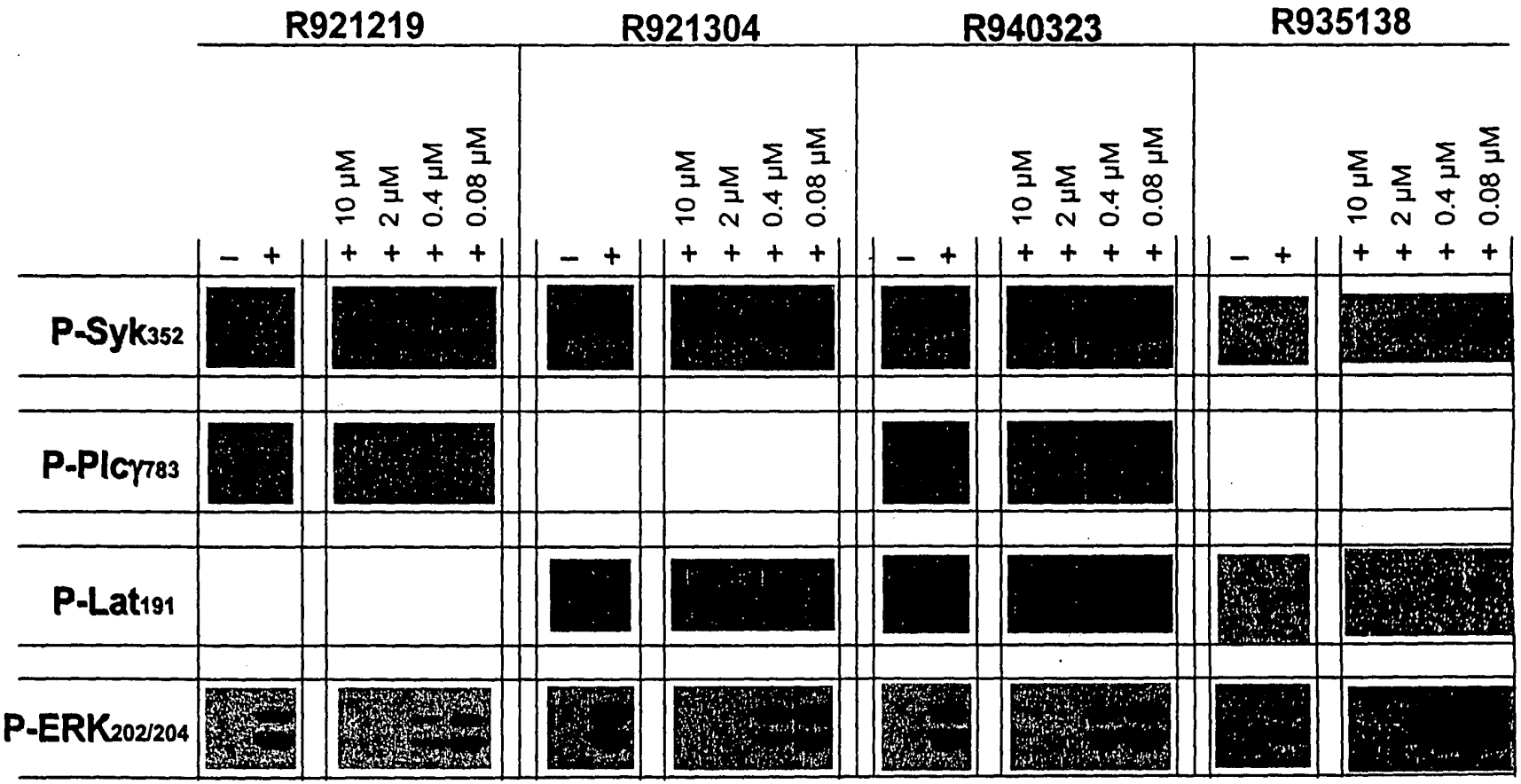


FIG. 11B

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

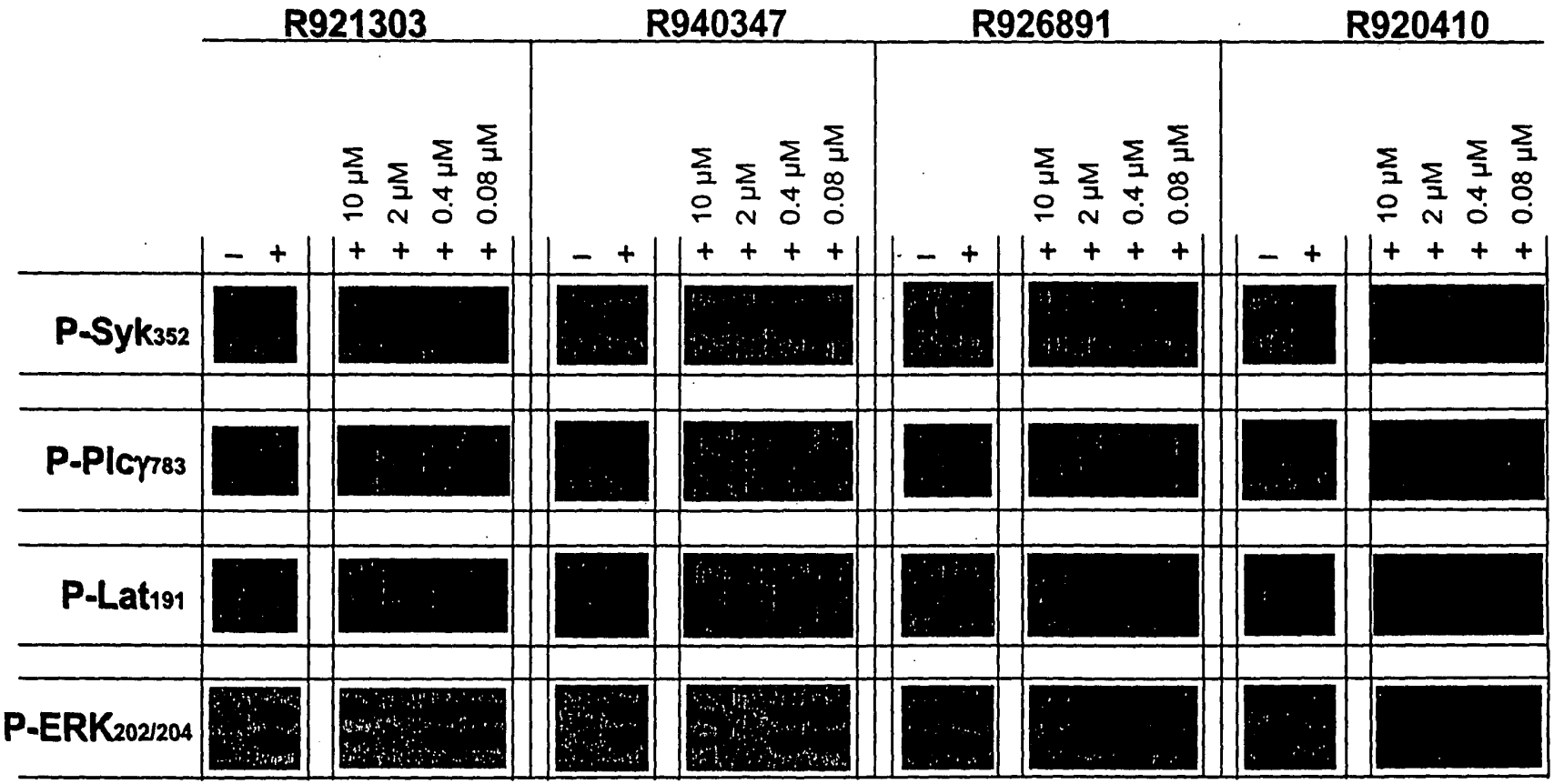


FIG. 11C

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

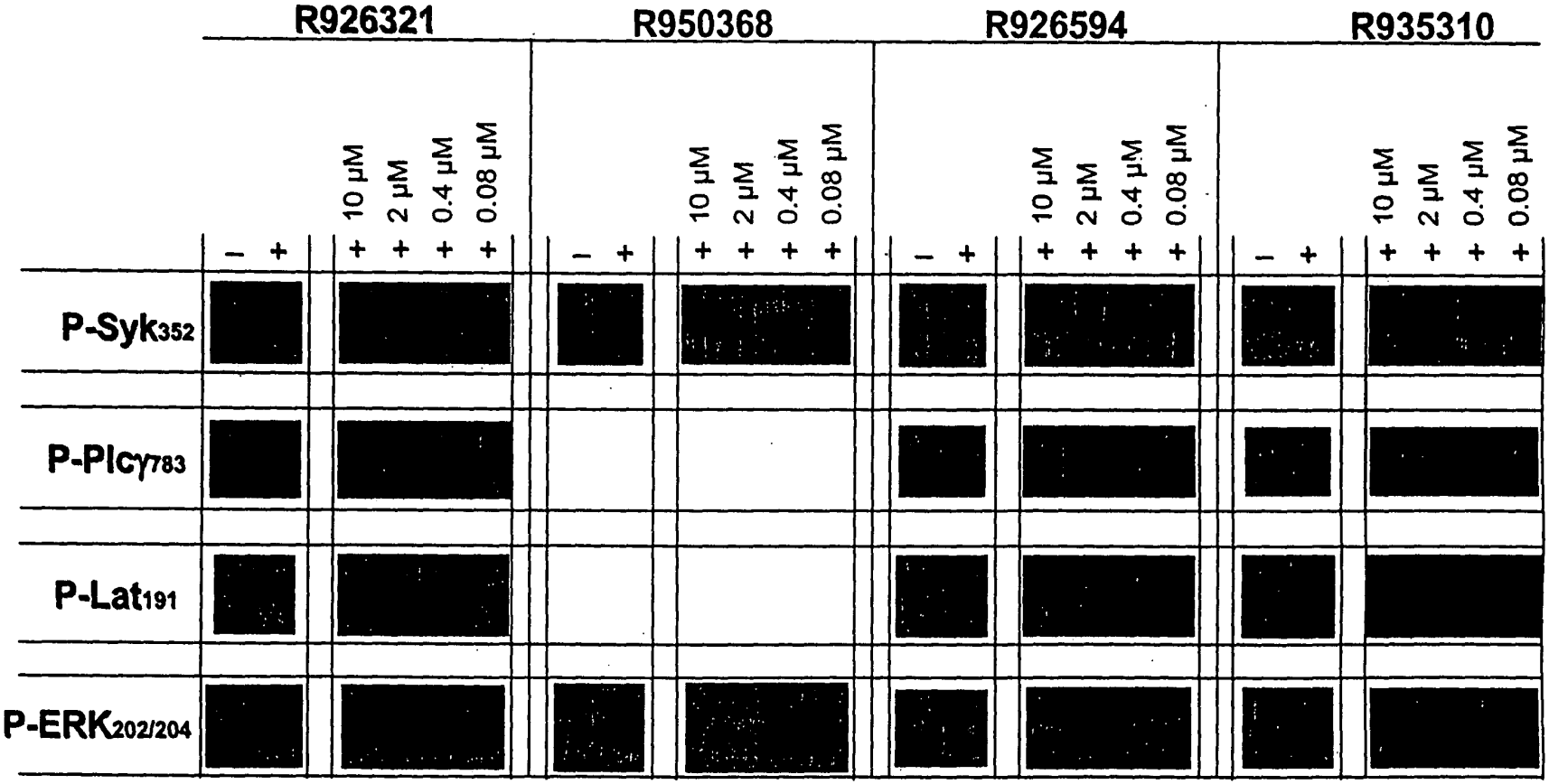


FIG. 11D

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

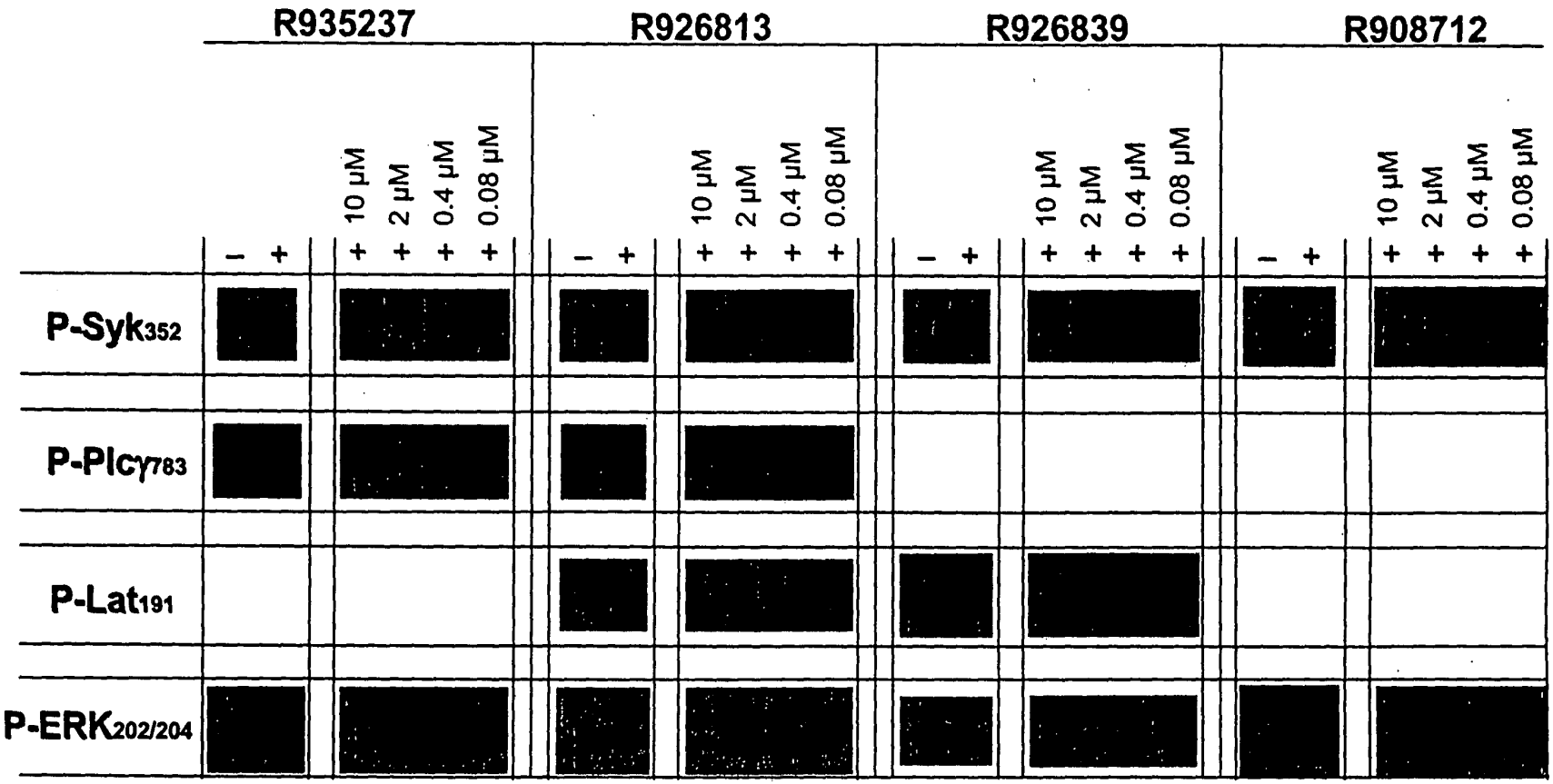


FIG. 12

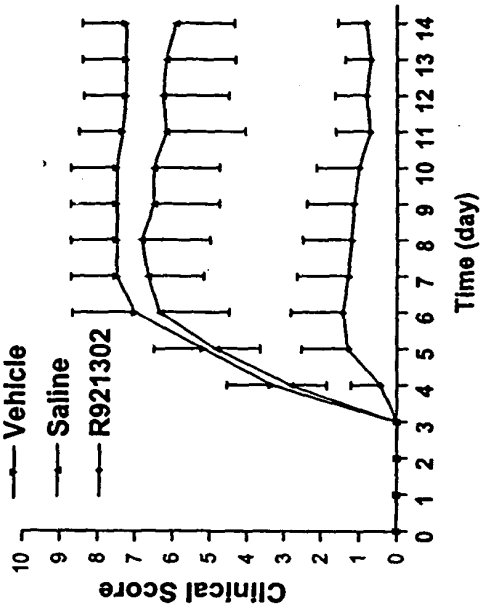

Effect of R921302 on CAIA
Vehicle
Saline
R921302
Clinical Score
Time (day)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14

FIG. 13

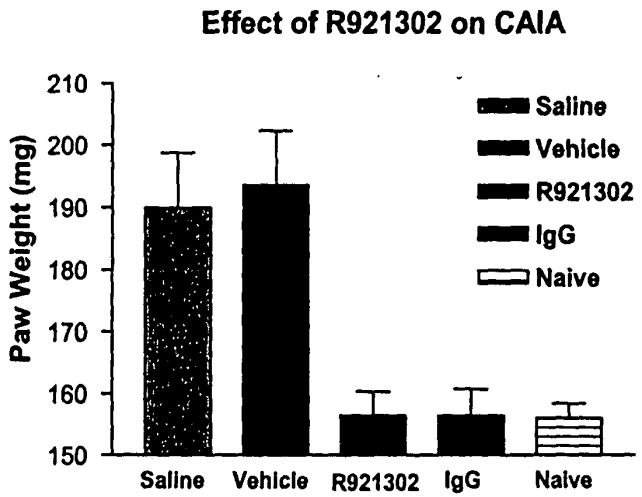

Effect of R921302 on CAIA
Paw Weight (mg)
210
200
190
180
170
160
150
Saline
Vehicle
R921302
IgG
Naive
Saline
Vehicle
R921302
IgG
Naive

FIG. 14

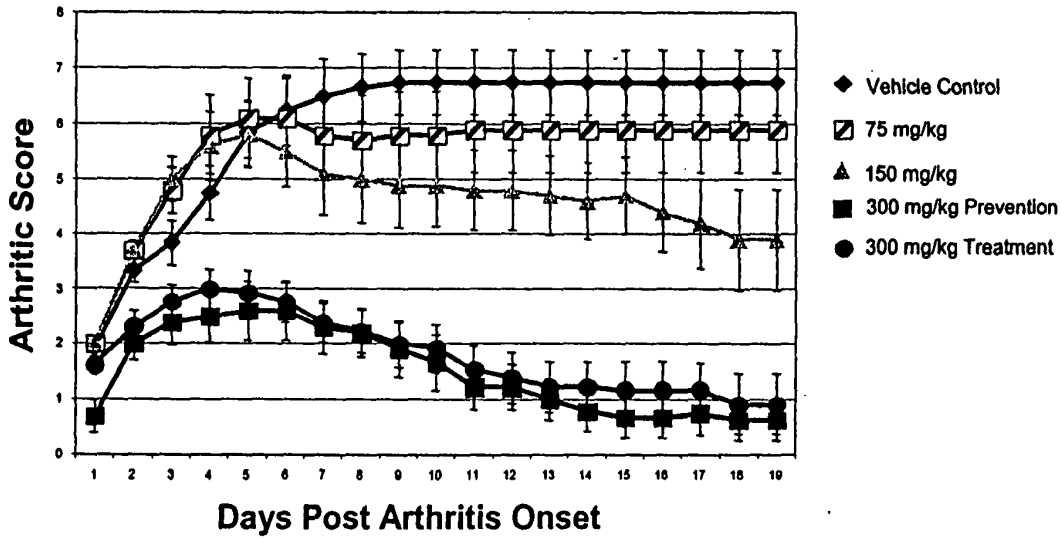

Arthritic Score
0
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Days Post Arthritis Onset
Vehicle Control
75 mg/kg
150 mg/kg
300 mg/kg Prevention
300 mg/kg Treatment

FIG. 15

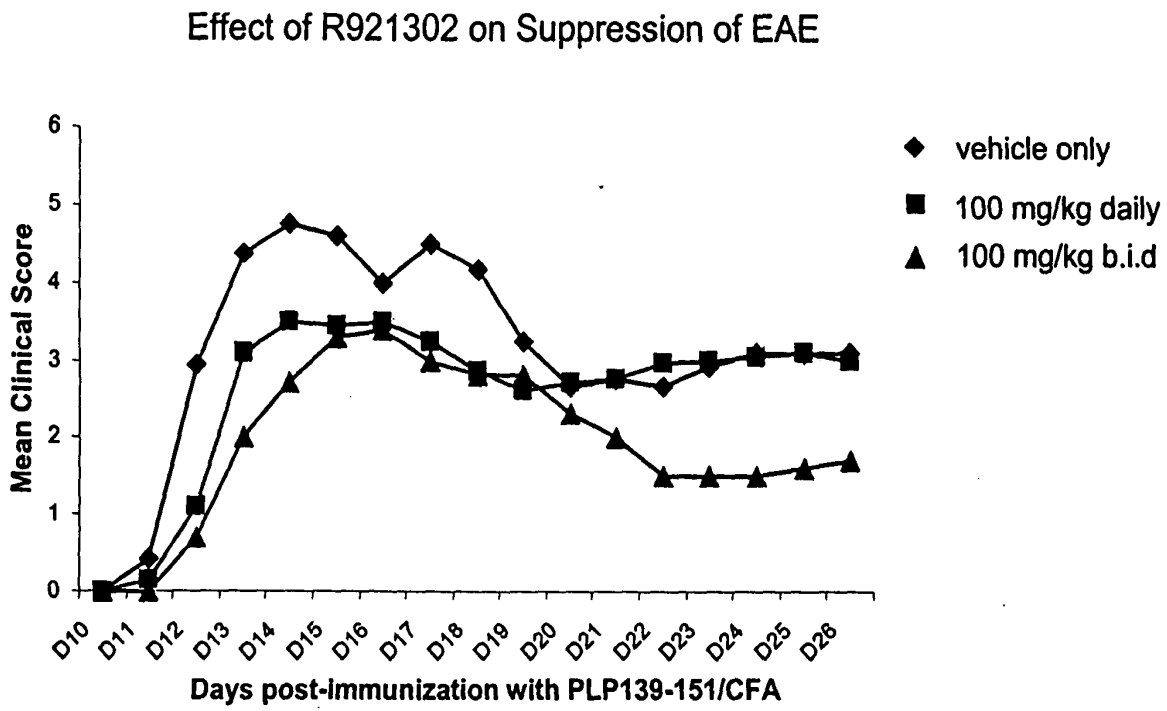
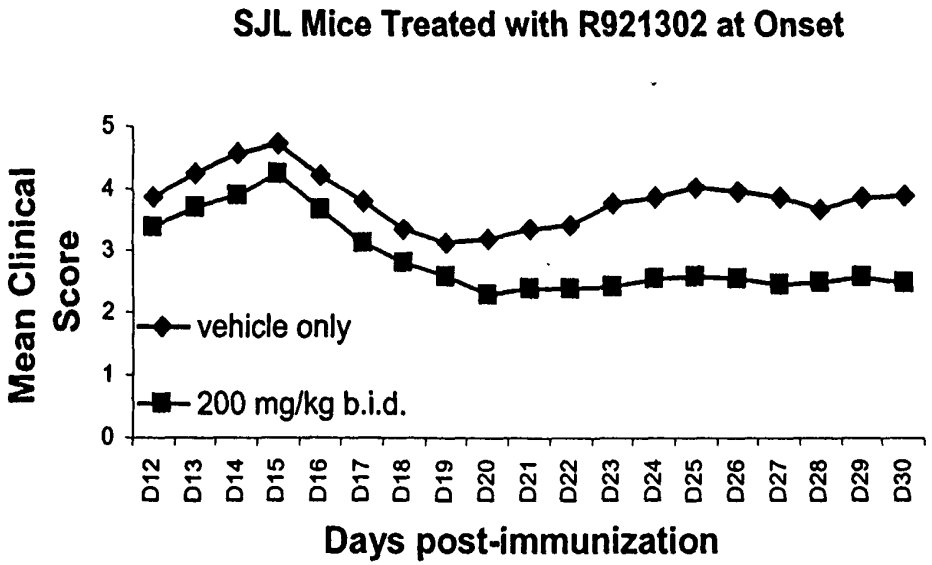

Effect of R921302 on Suppression of EAE
Mean Clinical Score
0
1
2
3
4
5
6
D10
D11
D12
D13
D14
D15
D16
D17
D18
D19
D20
D21
D22
D23
D24
D25
D26
Days post-immunization with PLP139-151/CFA
vehicle only
100 mg/kg daily
100 mg/kg b.i.d

FIG. 16


SJL Mice Treated with R921302 at Onset
Mean Clinical Score
0
1
2
3
4
5
vehicle only
200 mg/kg b.i.d.
D12
D13
D14
D15
D16
D17
D18
D19
D20
D21
D22
D23
D24
D25
D26
D27
D28
D29
D30
Days post-immunization